side effects, but it ameliorated the patients' symptoms to a certain extent. When fluvoxamine was coadministered with ethyl loflazepate or small doses of amoxapine for 1–2 months, patients exhibited signs of irritability and impulsive aggressive behaviour. No other antidepressants used in these cases induced such behaviour. Prompt discontinuation of fluvoxamine in cases 2 and 3 and the reduction of fluvoxamine by half and coadministration of fluoxetine in case 1 reversed the symptoms. In case 1, fluoxetine treatment did not elicit the aggressive behaviour that treatment with fluvoxamine did.

Serotonergic abnormalities have been proposed as a neurobiological basis for aggression and impulsivity.[3] The aggressive behaviour in these cases may be related to the fact that fluvoxamine is a more selective serotonin reuptake inhibitor than fluoxetine.[4] Some reports have described the beneficial effect of SSRIs on impulsivity and aggression.[5,6] However, we wish to draw attention to the emergence of paradoxical effects such as impulsivity and aggressive behaviour induced by fluvoxamine treatment.

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## Long-term treatment with clozapine in an adult with autistic disorder accompanied by aggressive behaviour

Recent clinical studies have reported beneficial effects of risperidone and olanzapine in autism and other pervasive developmental disorders,[1,2] but clozapine has received little attention.[3] We describe the effects of clozapine in an adult with autistic disorder accompanied by disruptive behaviour.

E.B., a 32-year-old man, was diagnosed with autism at the age of 2. Deficit of development of spoken language and profound mental retardation (IQ = 20) were observed, and managing temper tantrums, impulsive behaviour and self- and others-directed aggressiveness became impossible by the age of 18. The patient was admitted to hospital frequently for self-inflicted injuries and was repeatedly admitted to various institutions for harming his parents and destroying household items. Pharmacological mono- or multitherapy was unsatisfactory due to poor clinical efficacy and the emergence of extrapyramidal side effects, including severe dystonia. Drugs used for several months during the course of treatment included haloperidol (up to 50 mg/day), thioridazine (up to 600 mg/day) and clotiapine (40 mg/day), and diazepam (up to 15 mg/day) for several years.

At the time of initial observation, when he was 27, Clinical Global Impression (CGI) rating was 7 and clinician-rated Visual Analog Scale (VAS) scores were 95 for aggressiveness, 15 and 10 for social and eye contact, respectively, 82 for irritability and 12 for talkativeness.[2] Treatment with clozapine was initiated after routine ECG, EEG and blood tests, and was progressively increased, reaching the maintenance dose of 300 mg/day (100 mg at 8 am, 12 noon and 4 pm) within 6 weeks. Treatment continued throughout the 5-year period (age 27 to 32), during which time regular blood testing was done.

Clinical improvement was evident after 2 months of therapy. After 5 years of therapy, the patient showed marked improvement of aggressiveness and social interaction, and VAS scores were 15 for aggressiveness, 40 and 55 for social and eye contact, respectively, 35 for irritability and 45 for talkativeness. His CGI score was 4. Extrapyramidal side effects, white blood cell count changes, significant sedation or delayed reaction time were not observed. Self- and others-directed aggressiveness and temper tantrums are no longer observed. The patient's social skills, in terms of group interaction, meeting with unfamiliar people and simple monosyllabic dialog, have dramatically improved. Ritualistic behaviour is also moderately reduced (Yale–Brown obsessive–compulsive scale score was 11 compared with 17 before therapy).

Clinical and pharmacologic differences among the various atypical antipsychotic drugs have emerged.[4] Studies report that, compared with risperidone, clozapine is more effective on positive symptoms in chronic schizophrenia,[5] on Positive and Negative Syndrome Scale total scores and positive, negative, excitement, and cognitive factors,[6] as well as on CGI and CGI improvement.[7] In addition, clozapine appears particularly effective in reducing aggressive behaviour in patients with schizophrenia.[8]

Notably, with risperidone treatment, patients with schizophrenia improved significantly initially and remained stable thereafter, whereas patients taking clozapine showed a gradual improvement over the entire length of the trial.[6] Similarly, we observed progressive improvement throughout the 5-year treatment period. This is, to our knowledge, the first report of long-term treatment with an atypical antipsychotic for autism.

Pharmacologically, atypical antipsychotics show a higher antagonistic effect at serotonin 5-$HT_{2A}$ receptors and less of an effect at dopamine $D_2$ receptors, compared with classical antipsychotics.[4] Positron emission tomography imaging studies in humans indicate that clozapine, at clinically effective doses, presents a lower $D_2$ occupancy than typical antipsychotics, whereas $D_2$ occupancy of risperidone and olanzapine is similar to that of typical antipsychotics. This higher 5-$HT_{2A}$ / $D_2$ occupancy ratio of clozapine[9] may be relevant for autistic disorders; several studies suggest the involvement of 5-$HT_2$ and $D_2$ receptors in autism.[10,11] Notably, impaired serotonin synthesis in the frontal cortex, an area critical for language production, sensory integration and aggressive behaviour, has been reported in autism.[11] Electrophysiological data also point toward a unique profile of clozapine among atypical antipsychotic agents, due to its preferential 5-$HT_{2A}$ component, compared with risperidone.[12] This might be of functional significance because high serotonin levels have been associated with reduced drive for social attachments in animals,[13] and phencyclidine-induced social withdrawal in rats was significantly reversed by clozapine and olanzapine, but not by risperidone, raclopride or haloperidol.[14]

Taken together, preclinical and clinical observations suggest that clozapine stands out among atypical antipsychotic drugs, perhaps because of its unique pharmacological profile with a high 5-$HT_{2A}$ / $D_2$ occupancy ratio.[4] It is therefore tempting to speculate that clozapine may be particularly suitable for treating autistic disorders, especially in the presence of aggressiveness. This is a heuristic hypothesis worthy of further investigation.

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